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Chemoradiotherapy or Induction Chemotherapy Followed by Chemoradiotherapy University Hospital Fuenlabrada: Our Experience in 10 Years

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Retrospective descriptive study with 53 patients undergoing INDUCTION CHEMOTHERAPY + CRT vs CRT alone in which we analyze the tolerability, organ preservation, recurrence rates, overall survival (OS) and disease-free survival (DFS).

Within the group of induction (A), 86% (24/28) received 3 cycles TPF, while 14% (4/28) were treated with a doublet (platinum + taxol), being able to meet the treatment without delay or dose reduction of only 50%. Within non-induction group (B), 80% "RECEIVED all doses and without delay, while 20% (5/25) failed to finish, fell 80 % (4/5) of them.

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They are not comparable groups as the most important difference is that those with more advanced (N2 disease) are in group A (92.8% cT3-T4 or N2) versus Group B (32% cT3N0).

Conclusions:

- The Profile of our patients in the group of non-induction have more comorbidities and the earliest stages. Recurrence rates are similar in both groups, with a higher relapse and metastatic disease in the induction group (group A) because of more advanced tumors.
- We have to study new strategies for improving tolerance induction chemotherapy with cetuximab or nab-paclitaxel, and selecting best ones should receive concomitant cetuximab + RT.

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I. Introduction

Head and neck tumors represent in the United States an incidence of 52,610 cases and 60% are diagnosed at locally advanced stage.

Despite treatment aimed at eradicating the disease, the cure rates are still modest, especially in tumors not associated with human papillomavirus (HPV). Chemoradiotherapy (CRT) with Cisplatin 100 mg/m2 each 3 weeks showed an improvement in overall survival (OS) compared to radiotherapy (RT) [1]. Actually the controversy is between CRT vs induction chemotherapy (TPF= docetaxel 75 mg/m2, cisplatin 75 mg/m2, 5FU 750 mg/m2 by continuous infusion days 1-5) prior to CRT because it seems to **reduce distant recurrence without improving overall survival.** [2,3,4,5]

Our objectives are to describe what happens at the University Hospital of Fuenlabrada with 53 patients undergoing induction chemotherapy + CRT vs CRT alone, reflecting tolerability, organ preservation, recurrence rates, overall survival (OS) and disease free survival (DFS).

II. Material and Methods

We present a group of **53 patients**: 28 with induction treatment (cisplatin, 5-fluoracil, docetaxel) + CRT (group A) and 25 CRT or bioRT (group B: B1 cisplatin 100 mg/m2+ RT, B2 cetuximab 250 mg/m2+RT).

We performed a **descriptive retrospective study** and we analyzed tumor stage and nodes, gender, age, comorbidities, rates of relapses/ persistence disease, tolerability to treatment, organ preservation and survival (progression free survival and overall survival). We used SPSS statistic programme for the analyses.

Also **comparing our data** with published studies of induction chemotherapy: TTCC group, PARADIGM, DECIDE and GCTCC.

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III. Results

Variables	Induction chemo + CRT (group A) N=28	CRT or bioRT (group B) N=25
Treatment Induction Chemo	TPF x 3: 86 % Cisplatin+Taxolx3:14 %	
CRT	Cisplatin: 90% Cetuximab: 10%	Cisplatin: 60% Cetuximab: 40%
Radiotherapy Doses		
66-70 Gy	69%	84%
Unknown	21%	8%
Not finished	10%	8%
Tumor stage		
T2N2M0	7.1%	12%
T3N0M0	3.6%	32%
T3N2M0	21.4%	16%
T4N0M0	10.7%	16%
T4N1M0	10.7%	---
T4N2M0	42.9%	16%
Age(years)	56.9 (range 43-73)	62.2 (range 35-79)
Location		
Oropharynx	16%	46.4%
Larynx	56%	36%
Recurrence	(25%)	(20%)
→Metastasis	14.2%	4%
→Local and metastasis	7%	---
→Local	3.5%	16%
Persistence	35%	20%
Second primary tumours	7%	8%
Not relapsing	33%	48%
Median Survival		
Time to local recurrence (months)	55	21.5
Disease free survival (DFS) (months)	31.4	20
Overall survival(OS) (months)	46.8	32

Figure 1: Comparing analysed variables in induction chemotherapy + CRT vs CRT

a) Treatment

In group A; 86% (24/28) received 3 cycles of TPF, while 14% (4/28) were treated with a doublet (platin + taxol) because of bad tolerance to treatment. After induction, all of them received cisplatin + RT. However even having finished induction chemo, **only 50% completed** CRT without dosis delays.

In group B, the treatment could be cetuximab + RT or cisplatin + RT. **80% receive all doses without delays,** while 20% (5/25) could not finish it, relapsing 80% (4/5) of them.

According to the treatment received, in group B 40% (10/25) were treated with cetuximab, while 60% was cisplatin. The election of cetuximab was in those patients older, with comorbidities or renal impairment who we thought that they are not supporting chemo. In this group, treatment was even not finished in 3/10, with no relapsing in 2/10 and relapsing/persistence in 5/10.

According to RT, up to 10% could not complete treatment in both groups because of progression or bad tolerance. In group A: doses between 66-70Gy in 69%, 21% missing dates, 10% did not finish treatment or <30 Gy. In group B, 63-70 Gy in 84%, 8% missing dates and 8% 50 Gy.

b) Gender/age

Most of the patients in both groups are males, being younger in group A (media 56.9 years) than group B (media 62.2 years) with a similar age range in the two groups.

c) Toxic Habits/Comorbidities

More than 90% have smoking and drinking habit in both groups, with cardiovascular risk factors in 28.6% (group A) and 44% (group B). According to comorbidities (Charlson index), at least one factor was present in 25% of group A vs 44% in group B, being Charlson Index >5 points in most of them because of the tumour which sums 2 points.

d) Location

In group A, the first location is larynx (16% vs 56%), although in group B oropharynx is the most frequent organ affected (46.4% vs 36%)

e) Tumor stage

Firstly, the most important difference is that those with more advanced stage (N2 lymph node involvement) are in group A (92.8% cT3-T4 or N2) vs Group B (32% cT3N0).

f) Tumor recurrence

According to high percentage of advanced stage tumor in group A, it is easily to relapse as metastasic disease (14.2%=4/28 vs 4%=1/25 in group B). Detailing the 4 cases of metastasic relapse, we analysed another factors which could also influence. Initially 100% of them where T4N2, receiving 75% (3/4) of them 70 Gy, with unknown doses the other one (1/4). Persistence tumours are also T4N2-N0, with unknown doses of RT in 10% and less than 70% receive 70Gy, not receiving complete chemoradiotherapy in 20% of them.

In group B, **all of the relapses/persistent tumours** are T3-T4 N0-N2, with unknown RT doses in 10% of them, 50Gy in another 20%, comorbidities, synchronous tumour and older age in most of them.

g) Response by image

We have similar response rates (88%) in both groups, however we have more TC thant PET in group A because many patients are previosly to 2010 and PET/CT was not available in our Hospital. Another important date is that in the beginning we were not used to identify areas of inflammation with this technique, knowing nowadays that we have to wait for 12 weeks to be more exact and decide if what we see is tumor or not.

h) Survival

We have no enough patients to conclude, but it seems that our data in group A show a higher rate of metastatic, time to local recurrence (55 months vs 21.5 months), DFS (31.4 months vs 20 months) and OS (46.8 months vs 32 months).

i) Rescue surgery and organ preservation

Unable to perform organ preservation is only in 12.5% of cases. Rescue surgery is not need in 60% (A) and 72% (B); with surgery in both cases because of suspection of tumor persistence. In group A, 25% had neck dissection because of persistence tumour in PET that was not confirmed with histology. In group B, 20 % had neck dissection without malignancy histology.

We assume that this date is because in the beginning of "PET times", we were not used to identify areas of inflammation, knowing nowadays that we have to wait for 12 weeks to be more exact.

j) Tolerability

In group A and B mucositis grade II was achieved in all the patients, improving with dosis relays and topical treatment. In group a neutropenia was avoided with prophylactic G-CSF. As we previously reported, only 50% in group A could finish without doses reduction, while it was 80% in group B.

IV. Discussion

Comparing our results with literature it is well known that neoadjuvant chemotherapy (docetaxel + cisplatin + fluorouracil) (DCF) has achieved a reduction in the rate of distant recurrence [3,4,5], but it seems to not increase overall survival or progression-free survival.

Some important studies on induction QT are the TTCC group (Hitt et al), Boston (Haddad: PARADIGM study), Chicago (Cohen: DECIDE study) and GCTCC (Ghi), where the benefit in overall survival can only be achieved in the last one. [6,7,8,9]

Therefore no scheme is the same. If detailing the recent meta-analysis published in JCO and comparing with ours: [4]

- ✓ *Complete response in TPF group (33%)* vs 14% in PF. In our study, we have many patients valued by TC. In PET we have 10% complete response, adding 32.1% partial response also by PET and 46.4% partial or complete by TC.
- ✓ Median survival of **43 months.** The dose is kept to 91% of ciplatino, being almost 100% 5FU and paclitaxel. In ours: 46.8 months and dose kept in 86%.
- ✓ Published **DFS is 12.5 months**. Our data is 31.4 months.
- ✓ *Locoregional control 60.9%.* In our study, 33% do not relapse, 7% develop second primary tumours, with 35% persistent tumours (mostly rescued with ganglionar dissection) and only 25% of relapses.

So the question is how to select patients for induction chemotherapy. Data suggest that it would be more useful in those patients who need better locoregional control and have high risk of distant recurrence. As we have described, we have selected for induction chemotherapy those with less comorbities and advanced disease, **achieving good results** but with only 50% of complete treatment and no dosis delay.

Adding to these results, a recent meta-analysis has also described **that organ preservation** is greater in induction arm [9]. In our study, the percentages are similar between groups, needing surgery because of

suspection of tumor persistance, however in most of surgerys in group a malignancy is not conffirmed.

Finally, **we look for what can we do to improve tolerability. Some studies have developed to discern whether cetuximab + RT could be substituted for cisplatin + RT, with no conclusive results:** phase II studies (Pignon and Bonner) highlight HR 0.74 and modest effect on disease control in the distance first (Cisplatin) but not in the second. [1,10] A recent meta-analysis gives better results at 2 years on the arm of cisplatin + RT vs cetuximab + RT (OS 71% vs 60.7%, DFS 61.7% vs 43.1% and locoregional recurrence of 19.6% vs. 32.3%).[10,11]

Studies designed to improve induction tolerability with cetuximab (E1308 study: cetuximab + cisplatin + paclitaxel for 3 cycles) or nab paclitaxel (F II with cetuximab, nab paclitaxel, cisplatin and 5FU) are awaiting for results[12].

V. Conclusions

The profile of our patients in group B present more comorbidities and earlier stages than induction group. The recurrences rates is similar in both groups, with a higher relapse as metastatic disease in induction group (group A) because of more advanced tumors. Induction group overall survival is also better, however treatment tolerability with dosis delays is worse.

Persistence/Relapsing tumours happen in those patients with advanced stages, comorbidities, older age and not finishing RT (<60 Gy).

In the beginning, we perform neck dissection because of suspection of persistence tumour in PET/CT (initially not always performed after 12 weeks, which is now the standar to better discern inflammation vs tumor persistence), without conffirming malignancy with histology.

Induction chemotherapy has improved distance recurrence rates and organ preservation, with no differences in overall survival. However, in our opinion we must better target the profile of patients who would benefit of this treatment.

It is being studied new strategies for improving tolerance induction chemotherapy with cetuximab or nab-paclitaxel, and selecting better which ones must receive cetuximab + RT concomitant. It is a difficult issue to analyze, because we usually employ cetuximab in more fragile patients, being itself a negative prognostic factor.

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